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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/812,642	03/30/2004	Nikos Pagratis	NEX87/C2	5220

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EXAMINER	
VIVLEMORE, TRACY ANN	

ART UNIT	PAPER NUMBER
1635	

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06/25/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/812,642	PAGRATIS ET AL.	
	Examiner	Art Unit	
	Tracy Vivlemore	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 April 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Any rejection or objection not reiterated in this Action is withdrawn.

Response to arguments: Claim Rejections - 35 USC § 112

Claims 1-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for use of a nucleic acid ligand to TGFβ2 to inhibit TGFβ2-mediated proliferation of cultured cells, does not reasonably provide enablement for targeting a nucleic acid to a site in a patient, inhibition of TGFβ2 *in vivo* or treatment of a pathological condition mediated by TGFβ2 *in vivo* in any organism using a nucleic acid ligand to TGFβ2. This rejection is maintained for the reasons set forth in the office action mailed February 28, 2006.

Applicants traverse the scope of enablement rejection by asserting the delivery of nucleic acid ligands *in vivo* is not addressed in the Opalinska reference and this reference does not describe the state of the art with regard to nucleic acid ligands. Applicants argue Opalinska is limited to discussing the efficacy of nucleic acid gene therapy, nucleic acid ligands are not designed to work in a similar manner to that of nucleic acids for gene targeting, and the issues associated with the therapies are completely different. While it may be correct that nucleic acid ligands do not have a mechanism of action identical to that of antisense nucleic acids, nucleic acid ligands are nevertheless nucleic acids; difficulties encountered in delivery of nucleic acids to cells

would be the same for nucleic acid ligands as for antisense oligonucleotides. The teachings of Opalinska describe general unpredictability for delivery of nucleic acids and describe the fate of nucleic acids in cells.

Priority

No support could be found in the specifications of patents 5,475,096, 5,270,163, 5,660,985 or 5,496,938 for nucleic acid ligands targeted to TGF-β2 or methods of using such ligands. Applicant has not pointed out where these patents provide support for the claimed invention; therefore the priority date accorded the instant application remains June 2, 1995, the filing date of patent 5,731,424. .

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1 and 3-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gold et al. (US 5,270,163) in view of Tullis (WO 88/09810) and Shah et al. (Journal of Cell Science 1995).

The claims are directed to methods of inhibiting TGFβ2 by administration of a nucleic acid ligand targeted to TGFβ2. In specific embodiments, the nucleic acid ligand is conjugated to PEG that may have a molecular weight of 10-80K or 20-45K. These claims encompass embodiments wherein the TGFβ2 target is in a cell *in vitro* as well as embodiments wherein the TGFβ2 target is in a cell *in vivo*.

Gold et al. teach a method of identifying nucleic acid ligands by a process of *in vitro* selection and amplification. Targets for nucleic acid ligands (see column 13) include growth factors. Nucleic acid ligands are also referred to as nucleic acid antibodies and Gold et al. teach that nucleic acid ligands can be employed in diagnostics in a manner similar to conventional antibody-based diagnostics. Gold et al. also teach at column 9 that nucleic acid ligands have therapeutic uses as sequestering agents, drug delivery vehicles and modifiers of hormone action. Gold et al. do not teach conjugation of a nucleic acid ligand to PEG.

Tullis teaches nucleic acid conjugates comprising an antisense conjugated to a solubility-modifying moiety that may be hydrophobic and imparts amphiphilic character to the final product. At page 7 solubility-modifying moieties are taught as including polyethylene glycol as well as lipophilic compounds such as palmitate,

distearylglyceride and cholesteryl. Tullis teaches that the PEG has as many as 500 units, which would have a molecular weight within the ranges recited in the claims. Tullis teaches that the conjugates of the invention find use in drug delivery wherein the amphiphilic nature of the conjugate aids in transport across the cellular membrane.

Shah et al. teach at page 986, column 1 that TGFβ2 is one TGFβ isoform that has a role in cutaneous scarring. Shah et al. further teach on page 987 that inhibition of TGFβ2 through use of a neutralizing antibody reduced inflammatory response in healing wounds and reduced scarring.

It would have been obvious to one of ordinary skill in the art at the time of invention to make nucleic acid ligands taught by Gold et al. in order to target TGFβ2 and to use these ligands to inhibit a transforming growth factor β2 in cells *in vitro*. It would have been further obvious to one of ordinary skill to conjugate the ligands to a solubility modifying moiety such as PEG as taught by Tullis in order to improve cellular uptake. Gold et al. provide a motivation to use nucleic acid ligands in cells by teaching a method of isolating nucleic acid ligands to any target molecule, suggesting that growth factors are a desired target and by teaching that nucleic acid ligands can act in a fashion similar to antibodies. Shah et al. provide a motivation to target TGFβ2 by teaching its role in cutaneous scarring and that the neutralization of TGFβ2 by an antibody reduces scarring. Tullis provides a motivation to make conjugates of nucleic acids and solubility modifying moieties such as PEG, teaching that such conjugates are readily transported across cellular membrane. One of ordinary skill in the art would have had a reasonable expectation of success in producing a nucleic acid ligand to TGFβ2 because Gold et al.

teach that their method is applicable to almost any target. One of ordinary skill in the art would have had a reasonable expectation of success in making a conjugate of solubility modifying moiety and a nucleic acid ligand because Tullis teaches that such oligonucleotide conjugates can be made using routine synthesis methods.

Thus, the invention of claims 1 and 3-5 would have been obvious, as a whole, at the time of invention.

Response to Arguments

Applicants traverse the 103 rejection by arguing that while the term nucleic acid ligand antibody has been used in order to delineate the mode of action of a nucleic acid ligand the nucleic acid ligand is not an antibody and predicting the ability of a nucleic acid ligand to target TGFβ2 is not obvious. Applicants further argue that binding in the present invention is through a nucleic acid/growth factor interaction whereas Shah et al. describes an antibody/growth factor interaction. This argument appears to be directed to motivation to combine the references and applicant appears to be relying on the differences between antibodies and nucleic acid ligands to argue there is no motivation. While it is correct that nucleic acid ligands are not antibodies, Gold et al. explicitly teach that nucleic acid ligands have the same use as antibodies and provide a motivation to use nucleic acid ligands by explicitly teaching at column 9 that nucleic acid ligands have therapeutic uses as sequestering agents, drug delivery vehicles and modifiers of hormone action.

Applicants further assert the addition of PEG is not obvious, arguing that the teachings of Tullis are limited to conjugates having an increased ability to be

transported across the cellular membrane while the present invention is directed towards an extracellular moiety, TGFβ2, and the ability to cross the cellular membrane is not an issue. This argument is not persuasive because TGFβ2 may ultimately act extracellularly it is made within cells and exists intracellularly as well. While applicants assert TGFβ2 is an extracellular moiety the claims are not limited to extracellular embodiments. Applicants further assert the teachings of Tullis to utilize conjugates for enhanced membrane transport or stability with regard to exonuclease digestion are not applicable because the present invention teaches the use of conjugates for modifications yielding a higher stability in serum and animals. This is not persuasive because the teachings of Tullis are applicable to the instant invention; Tullis teaches that nucleic acid conjugates are also resistant to nucleases, which provides increased serum stability.

Applicants submit that there is no prediction of success for the instant invention from the teachings of Gold et al. and Tullis. This is not correct, the reasonable expectation of success in producing a nucleic acid ligand to TGFβ2 is provided by Gold et al, who teach their method of producing nucleic acid ligands is applicable to almost any target. The reasonable expectation of success in making a conjugate of solubility modifying moiety and a nucleic acid ligand is provided by Tullis, who teaches that such oligonucleotide conjugates can be made using routine synthesis methods.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, J. Douglas Schultz, can be reached on 571-272-0763. The central FAX Number is 571-273-8300.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Tracy Vivlemore
Examiner
Art Unit 1635

TV
June 18, 2007

RICHARD SCHNIZER, PH.D.
PRIMARY EXAMINER